17th Edition

HARRISON'S

Principles of INTERNAL MEDICINE

Fauci • Braunwald • Kasper • Hauser
Longo • Jameson • Loscalzo

Volume II

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17th Edition

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Principles of INTERNAL MEDICINE

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ASTHMA

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Asthma is defined as a chronic inflammatory disease of airways that is characterized by increased responsiveness of the tracheobronchial tree to a multiplicity of stimuli. It is manifested physiologically by a widespread narrowing of the air passages, which may be relieved spontaneously or as a result of therapy, and clinically by paroxysms of dyspnea, cough, and wheezing. Asthma is an episodic disease, with acute exacerbations interspersed with symptom-free periods. Typically, most attacks are short-lived, lasting minutes to hours, and clinically the patient seems to recover completely after an attack. However, there can be a phase in which the patient experiences some degree of airway obstruction daily. This phase can be mild, with or without superimposed severe episodes, or much more serious, with severe obstruction persisting for days or weeks; the latter condition is known as *status asthmaticus*. In unusual circumstances, acute episodes can cause death.

PREVALENCE AND ETIOLOGY Asthma is a very common disease with immense social impact. The prevalence of asthma is rising in many parts of the world, but it is unclear whether this is due to an actual increase in incidence or merely to the fact that the size of the overall population is growing. It is estimated that 4 to 5% of the population of the United States is affected. Data from the Centers for Disease Control and Prevention suggest that 10 to 11 million persons had acute attacks in 1998, which resulted in 13.9 million outpatient visits, 2 million requests for urgent care, and 423,000 hospitalizations, with a total cost >$6 billion. The impact of the disease appears to fall more heavily on minorities and inner-city African-American and Hispanic persons.

Bronchial asthma occurs at all ages but predominantly in early life. About one-half of cases develop before age 10, and another third occur before age 40. In childhood, there is a 2:1 male/female preponderance, but the sex ratio equalizes by age 30. From an etiologic standpoint, asthma is a heterogeneous disease and genetic (atopic) and environmental factors, such as viruses, occupational exposures, and allergens, contribute to its initiation and continuance.

Atopy is the single largest risk factor for the development of asthma. *Allergic asthma* is often associated with a personal and/or family history of allergic diseases such as rhinitis, urticaria, and eczema; with positive wheal-and-flare skin reactions to intradermal injection of extracts of airborne antigens; with increased levels of IgE in the serum; and/or with a positive response to provocation tests involving the inhalation of specific antigen.

A significant fraction of patients with asthma present with no personal or family history of allergy, with negative skin tests, and with normal serum levels of IgE, and therefore have disease that cannot be classified on the basis of currently defined immunologic mechanisms. These patients are said to have *idiosyncratic asthma* or *nonatopic asthma*. Many patients have disease that does not fit clearly into either of the preceding categories but instead falls into a mixed group with features of each. In general, asthma that has its onset in early life tends to have a strong allergic component, whereas asthma that develops late tends to be nonallergic or to have a mixed etiology.

PATHOGENESIS (See also Chap. 298) Asthma results from a state of persistent subacute inflammation of the airways. Even in asymptomatic patients, the airways can be edematous and infiltrated with eosinophils, neutrophils, and lymphocytes, with or without an increase in the collagen content of the epithelial basement membrane. Overall, there is a generalized increase in cellularity associated with an elevated capillary density. There may also be glandular hypertrophy and denudation of the epithelium. These changes may persist despite treatment and often do not relate to the severity of the disease.

The physiologic and clinical features of asthma derive from an interaction among the resident and infiltrating inflammatory cells in the airway surface epithelium, inflammatory mediators, and cytokines. The cells thought to play important parts in the inflammatory response are mast cells, eosinophils, lymphocytes, and airway epithelial cells. The roles of neutrophils, macrophages, and other cellular constituents of the airways are less well defined. Each of the major cell types can contribute mediators and cytokines to initiate and amplify both acute inflammation and the long-term pathologic changes described (Fig. 236-1). The mediators released produce an intense, immediate inflammatory reaction involving bronchoconstriction, vascular congestion, edema formation, increased mucus production, and impaired mucociliary transport. This intense local event can then be followed by a more chronic one. Other elaborated chemotactic factors (eosinophil and neutrophil chemotactic factors of anaphylaxis and leukotriene B_4) also bring eosinophils, platelets, and polymorphonuclear leukocytes to the site of the reaction. The airway epithelium is both the target of, and a contributor to, the inflammatory cascade. This tissue both amplifies bronchoconstriction and promotes vasodilatation through the release of the compounds shown in Fig. 236-2.

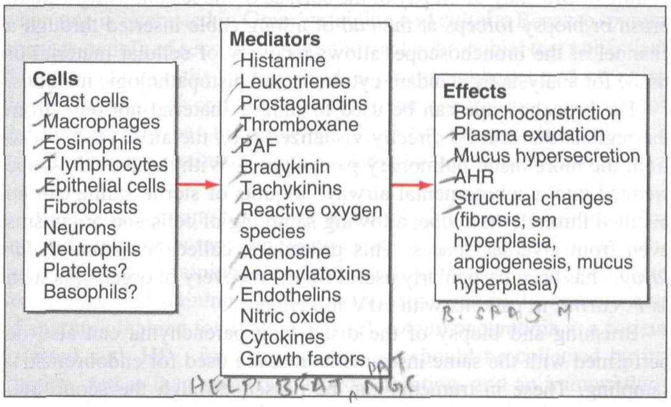

FIGURE 236-1 Cellular sources of inflammatory mediators and their physiologic effects. PAF, platelet-activating factor; AHR, antihyaluronidase reaction. [*From PJ Barnes, in E Middleton et al (eds): Allergy Principles and Practice, 5th ed. St. Louis, Mosby, 1998, with permission.*]

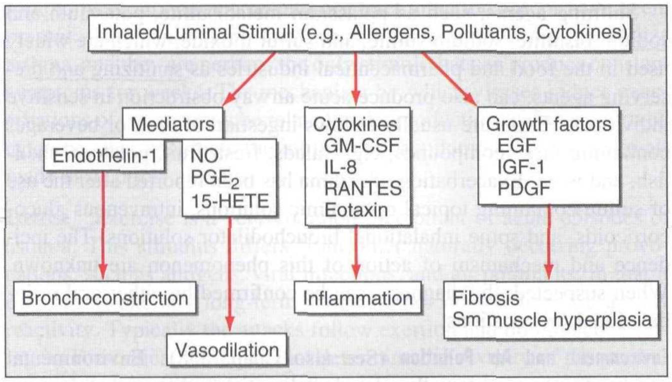

FIGURE 236-2 Inflammatory mediators derived from epithelial sources. NO, nitrous oxide; PGE_2, prostaglandin E_2; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; RANTES, regulated on activation, T cell expressed and secreted; EGF, epidermal growth factor; IGF, insulin-like growth factor; PDGF, platelet-derived growth factor. [*From PJ Barnes, in E Middleton et al (eds): Allergy Principles and Practice, 5th ed. St. Louis, Mosby, 1998, with permission.*]

The eosinophil appears to play an important part in the infiltrative component. Interleukin (IL) 5 stimulates the release of these cells into the circulation and extends their survival. Once activated, these cells are a rich source of leukotrienes, and the granular proteins released (major basic protein and eosinophilic cationic protein) and oxygen-derived free radicals are capable of destroying the airway epithelium, which then is sloughed into the bronchial lumen in the form of Creola bodies. Besides resulting in a loss of barrier and secretory function, such damage elicits the production of chemotactic cytokines, leading to further inflammation. In theory, it can also expose sensory nerve endings, thus initiating neurogenic inflammatory pathways. That, in turn, could convert a primary local event into a generalized reaction via a reflex mechanism. Although an important element in inflammation, the role that the eosinophil plays in establishing and maintaining airway hyperresponsiveness is undergoing reevaluation. Studies using antibodies against IL-5 show a disassociation between the inflammatory and physiologic events following an antigen challenge and blood and sputum eosinophilia. The cytokine network possibly involved in asthma is shown in Fig. 236-3.

T lymphocytes also appear to be important in the inflammatory response. Activated T_H2 cells are present in increased numbers in asthmatic airways and produce cytokines such as IL-4 that initiate humoral (IgE) immune responses. They also elaborate IL-5 with its effect on eosinophils. Data are accumulating that asthma may be related to an imbalance between T_H1 and T_H2 immune responses, but firm conclusions are not yet available.

GENETIC CONSIDERATIONS Although there is little doubt that asthma has a strong familial component, the identification of the genetic mechanisms underlying the illness has proven difficult for such fundamental reasons as a lack of uniform agreement on the definition of the disease, the inability to define a single phenotype, non-Mendelian modes of inheritance, and an incomplete understanding of how environmental factors modify genetic expression. Screening families for candidate genes has identified multiple chromosomal regions that relate to atopy, elevated IgE levels, and airway hyperresponsiveness. Evidence for genetic linkage of high total serum IgE levels and atopy has been observed on chromosomes 5q, 11q, and 12q in a number of populations scattered throughout the world. Regions of the genome demonstrating evidence for linkage to bronchial hyperreactivity also typically show evidence for linkage to elevated total serum IgE levels. Excellent candidate genes exist for specific abnormalities in asthma within the regions that were identified in the linkage studies. For example, chromosome 5q contains cytokine clusters including IL-4, IL-5, IL-9, and IL-13. Other regions on chromosome 5q also contain the β-adrenergic receptors and the glucocorticoid receptors. Chromosome 6p contains regions that are important in antigen presentation and mediation of the inflammatory response. Chromosome 12q contains two genes that could influence atopy and airway hyperresponsiveness, including nitric oxide synthase.

STIMULI THAT INCITE ASTHMA The stimuli that incite acute episodes of asthma can be grouped into seven major categories: allergenic, pharmacologic, environmental, occupational, infectious, exercise-related, and emotional.

Allergens Allergic asthma is dependent on an IgE response controlled by T and B lymphocytes and activated by the interaction of antigen with mast cell–bound IgE molecules. The airway epithelium and submucosa contain dendritic cells that capture and process antigen. After taking up an immunogen, these cells migrate to the local lymph nodes where they present the material to T cell receptors. In the appropriate genetic setting, the interaction of antigen with a naïve T cell T_H0 in the presence of IL-4 leads to the differentiation of the cell to a T_H2 subset. This process not only helps facilitate the inflammation of asthma but also causes B lymphocytes to switch their antibody production from IgG and IgM to IgE.

Once synthesized and released by B cells, IgE circulates in the blood until it attaches to high-affinity receptors on mast cells and low-affinity receptors on basophils. Most of the allergens that provoke asthma are airborne, and to induce a state of sensitivity they must be reasonably abundant for considerable periods of time. Once sensitization has occurred, however, the patient can exhibit exquisite responsivity, so that minute amounts of the offending agent can produce significant exacerbations of the disease. Immune mechanisms appear to be causally related to the development of asthma in 25 to 35% of all cases and to be contributory in perhaps another third. Higher prev-

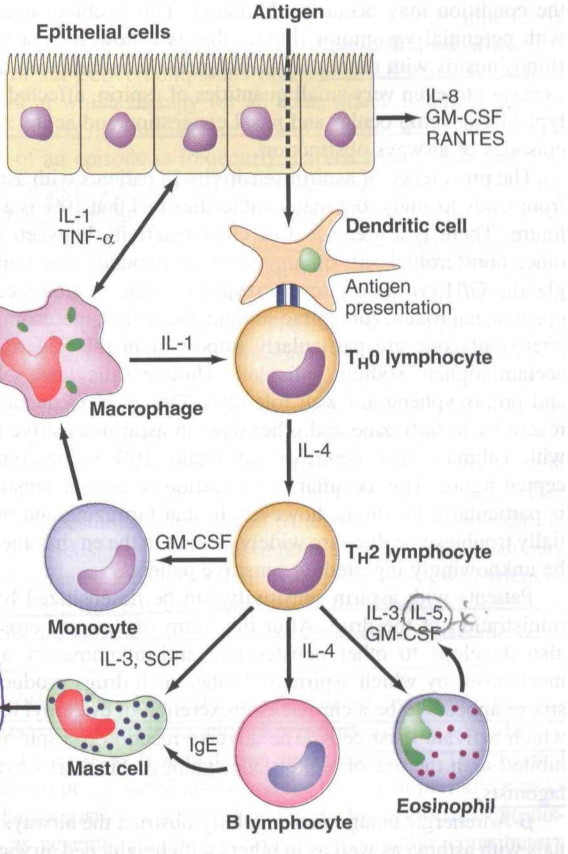

FIGURE 236-3 Cytokine network in allergic asthma. IL, interleukin; GM-CSF, granulocyte-macrophage colony-stimulating factor; RANTES, regulated on activation, T cell expressed and secreted; TNF, tumor necrosis factor; SCS, stem cell factor. [*From PJ Barnes, in E Middleton et al (eds): Allergy Principles and Practice, 5th ed. St. Louis, Mosby, 1998, with permission.*]

alences have been suggested, but it is difficult to know how to interpret the data because of confounding factors. Allergic asthma is frequently seasonal, and it is most often observed in children and young adults. A nonseasonal form may result from allergy to feathers, animal danders, dust mites, molds, and other environmental antigens that are present continuously. Exposure to antigen typically produces an immediate response in which airway obstruction develops in minutes and then resolves. In 30 to 50% of patients, a second wave of bronchoconstriction, the so-called late reaction, develops 6 to 10 h later. In a minority, only a late reaction occurs. It was formerly thought that the late reaction was essential to the development of the increase in airway reactivity that follows antigen exposure. This is now known not to be the case.

The mechanism by which an inhaled allergen provokes an acute episode of asthma depends in part on antigen-antibody interactions on the surface of pulmonary mast cells, with the subsequent generation and release of the mediators of immediate hypersensitivity. Current hypotheses hold that very small antigenic particles penetrate the lung's defenses and come in contact with mast cells that interdigitate with the epithelium at the luminal surface of the central airways. The subsequent elaboration of mediators and cytokines then produces the sequence outlined above.

Pharmacologic Stimuli The drugs most commonly associated with the induction of acute episodes of asthma are aspirin, coloring agents such as tartrazine, β-adrenergic antagonists, and sulfiting agents. It is important to recognize drug-induced bronchial narrowing because its presence is often associated with great morbidity. Furthermore, death sometimes has followed the ingestion of aspirin (or other nonsteroidal anti-inflammatory agents) or β-adrenergic antagonists. The typical aspirin-sensitive respiratory syndrome primarily affects adults, although the condition may occur in childhood. This problem usually begins with perennial vasomotor rhinitis that is followed by a hyperplastic rhinosinusitis with nasal polyps. Progressive asthma then appears. On exposure to even very small quantities of aspirin, affected individuals typically develop ocular and nasal congestion and acute, often severe episodes of airways obstruction.

The prevalence of aspirin sensitivity in patients with asthma varies from study to study, but many authorities feel that 10% is a reasonable figure. There is a great deal of cross-reactivity between aspirin and other nonsteroidal anti-inflammatory compounds that inhibit prostaglandin G/H synthase 1 (cyclooxygenase type 1). Indomethacin, fenoprofen, naproxen, zomepirac sodium, ibuprofen, mefenamic acid, and phenylbutazone are particularly important in this regard. However, acetaminophen, sodium salicylate, choline salicylate, salicylamide, and propoxyphene are well tolerated. The exact frequency of cross-reactivity to tartrazine and other dyes in aspirin-sensitive individuals with asthma is also controversial; again, 10% is the commonly accepted figure. This peculiar complication of aspirin-sensitive asthma is particularly insidious, however, in that tartrazine and other potentially troublesome dyes are widely present in the environment and may be unknowingly ingested by sensitive patients.

Patients with aspirin sensitivity can be desensitized by daily administration of the drug. After this form of therapy, cross-tolerance also develops to other nonsteroidal anti-inflammatory agents. The mechanism by which aspirin and other such drugs produce bronchospasm appears to be a chronic overexcretion of cysteinyl leukotrienes, which activate mast cells. The adverse reaction to aspirin can be inhibited with the use of leukotriene synthesis blockers or receptor antagonists.

β-Adrenergic antagonists regularly obstruct the airways in individuals with asthma as well as in others with heightened airway reactivity and should be avoided by such individuals. Even the selective beta$_1$ agents have this propensity, particularly at higher doses. In fact, the local use of beta$_1$ blockers in the eye for the treatment of glaucoma has been associated with worsening asthma.

Sulfiting agents, such as potassium metabisulfite, potassium and sodium bisulfite, sodium sulfite, and sulfur dioxide, which are widely used in the food and pharmaceutical industries as sanitizing and preserving agents, can also produce acute airway obstruction in sensitive individuals. Exposure usually follows ingestion of food or beverages containing these compounds, e.g., salads, fresh fruit, potatoes, shellfish, and wine. Exacerbation of asthma has been reported after the use of sulfite-containing topical ophthalmic solutions, intravenous glucocorticoids, and some inhalational bronchodilator solutions. The incidence and mechanism of action of this phenomenon are unknown. When suspected, the diagnosis can be confirmed by either oral or inhalational provocations.

Environment and Air Pollution (See also Chap. 238) Environmental causes of asthma are usually related to climatic conditions that promote the concentration of atmospheric pollutants and antigens. These conditions tend to develop in heavily industrial or densely populated urban areas and are frequently associated with thermal inversions or other situations creating stagnant air masses. In these circumstances, although the general population can develop respiratory symptoms, patients with asthma and other respiratory diseases tend to be more severely affected. The air pollutants known to have this effect are ozone, nitrogen dioxide, and sulfur dioxide. All produce greater effects during periods of high ventilation. In some regions of North America, seasonal concentrations of airborne antigens such as pollen can rise high enough to result in epidemics of asthma admissions to hospitals and an increase in the death rate. These events may be ameliorated by treating patients prophylactically with anti-inflammatory drugs before the allergy season begins.

Occupational Factors (See also Chap. 238) Occupation-related asthma is a significant health problem, and acute and chronic airway obstruction have been reported to follow exposure to a large number of compounds used in many types of industrial processes. In general, the agents can be classified into high-molecular-weight compounds, which are believed to induce asthma through immunologic mechanisms, and low-molecular-weight agents, which serve as haptines or can release bronchoconstrictor substances. High-molecular-weight compounds of importance are *wood and vegetable dusts* (e.g., those of oak, grain, flour, castor bean, green coffee bean, mako, gum acacia, karay, gum, and tragacanth), *pharmaceutical agents* (e.g., antibiotics, piperazine, and cimetidine), *biologic enzymes* (e.g., laundry detergents, pancreatic enzymes, and *Bacillus subtilis*), and *animal and insect dusts, serums, and secretions* (e.g., laboratory animals, chickens, crabs, prawns, oysters, flys, bees, and moths). Troublesome low-molecular-weight compounds are *metal salts* (e.g., platinum, chrome, vanadium, and nickel) and *industrial chemicals and plastics* (e.g., toluene diisocyanate, phthalic acid anhydride, trimellitic anhydride, persulfates, ethylenediamine, *p*-phenylenediamine, western red cedar, azidrocarbonamide, and various dyes). Formaldehyde and urea formaldehyde also fall into this group. It is important to recognize that exposure to sensitizing chemicals, particularly those used in paints, solvents, and plastics, can also occur during leisure or non-work-related activities.

If the occupational agent causes an immediate or dual immunologic reaction, the history is similar to that which occurs with exposure to other antigens. Often, however, patients will give a characteristic cyclic history. They are well when they arrive at work, and symptoms develop toward the end of the shift, progress after the work site is left, and then regress. Absence from work during weekends or vacations brings about remission. Frequently, there are similar symptoms in fellow employees.

Infections Respiratory infections are the most common of the stimuli that evoke acute exacerbations of asthma. Respiratory viruses and not bacteria or allergy to microorganisms are the major etiologic factors. In young children, the most important infectious agents are respiratory syncytial virus and parainfluenza virus. In older children and adults, rhinovirus and influenza virus predominate as pathogens. Simple colonization of the tracheobronchial tree is insufficient to evoke acute episodes of bronchospasm, and attacks of asthma occur only when symptoms of an ongoing respiratory tract infection are, or have been, present. Viral infections can actively and chronically destabilize asthma, and they are perhaps the only stimuli that can produce constant symptoms for weeks. The mechanism by which viruses induce exacerbations of asthma may be related to the production of T cell–derived cytokines that potentiate the infiltration of inflammatory cells into already susceptible airways.

Exercise Exercise is a very common precipitant of acute episodes of asthma. This stimulus differs from other naturally occurring provocations, such as antigens, viral infections, and air pollutants, in that it does not evoke any long-term sequelae, nor does it increase airway reactivity. Typically the attacks follow exertion and do not occur during it. The critical variables that determine the severity of the postexertional airway obstruction are the levels of ventilation achieved and the temperature and humidity of the inspired air. The higher the ventilation and the lower the heat content of the air, the greater the response. For the same inspired air conditions, running produces a more severe attack of asthma than walking because of its greater ventilatory cost. Conversely, for a given task, the inhalation of cold air markedly enhances the response, while warm, humid air blunts or abolishes it. Consequently, activities such as ice hockey, cross-country skiing, and ice skating (high ventilations of cold air) are more provocative than is swimming in an indoor, heated pool (relatively low ventilation of humid air). The mechanism by which exercise produces obstruction may be related to a thermally produced hyperemia and capillary leakage in the airway wall.

Emotional Stress Psychological factors can worsen or ameliorate asthma. Changes in airway caliber seem to be mediated through modification of vagal efferent activity, but endorphins may also play a role. The extent to which psychological factors participate in the induction and/or continuation of any given acute exacerbation is not established but probably varies from patient to patient and in the same patient from episode to episode.

PATHOLOGY In a patient who has died of acute asthma, the most striking feature of the lungs at necropsy is their gross overdistention and failure to collapse when the pleural cavities are opened. When the lungs are cut, numerous gelatinous plugs of exudate are found in most of the bronchial branches down to the terminal bronchioles. Histologic examination shows hypertrophy of the bronchial smooth muscle, hyperplasia of mucosal and submucosal vessels, mucosal edema, denudation of the surface epithelium, pronounced thickening of the basement membrane, and eosinophilic infiltrates in the bronchial wall. There is an absence of any of the well-recognized forms of destructive emphysema.

PATHOPHYSIOLOGY The pathophysiologic hallmark of asthma is a reduction in airway diameter brought about by contraction of smooth muscle, vascular congestion, edema of the bronchial wall, and thick, tenacious secretions. The net result is an increase in airway resistance, a decrease in forced expiratory volumes and flow rates, hyperinflation of the lungs and thorax, increased work of breathing, alterations in respiratory muscle function, changes in elastic recoil, abnormal distribution of both ventilation and pulmonary blood flow with mismatched ratios, and altered arterial blood gas concentrations. Thus, although asthma is considered to be primarily a disease of airways, virtually all aspects of pulmonary function are compromised during an acute attack. In addition, in very symptomatic patients there frequently is electrocardiographic evidence of right ventricular hypertrophy and pulmonary hypertension. When a patient presents for therapy, the 1-s forced expiratory volume (FEV_1) or peak expiratory flow rate (PEFR) is typically $<40\%$ of predicted. In keeping with the alterations in mechanics, the associated air trapping is substantial. In acutely ill patients, residual volume frequently approaches 400% of normal, while functional residual capacity doubles.

Hypoxia is a universal finding during acute exacerbations, but frank ventilatory failure is relatively uncommon, being observed in 10 to 15% of patients presenting for therapy. Most individuals with asthma have hypocapnia and a respiratory alkalosis. In acutely ill patients, the finding of a normal arterial carbon dioxide tension tends to be associated with quite severe levels of obstruction. Consequently, when found in a symptomatic individual, it should be viewed as representing impending respiratory failure, and the patient should be treated accordingly. Equally, the presence of metabolic acidosis in the setting of acute asthma signifies severe obstruction. Cyanosis is a very late sign. Trying to judge the state of an acutely ill patient's ventilatory status on clinical grounds alone can be extremely hazardous, and clinical indicators should not be relied on with any confidence. Therefore, in patients with suspected alveolar hypoventilation, arterial blood gas tensions must be measured.

CLINICAL FEATURES The symptoms of asthma consist of a triad of dyspnea, cough, and wheezing, the last often being regarded as the sine qua non. In its most typical form, all three symptoms coexist. At the onset of an attack, patients experience a sense of constriction in the chest, often with a nonproductive cough. Respiration becomes audibly harsh; wheezing in both phases of respiration becomes prominent; expiration becomes prolonged; and patients frequently have tachypnea, tachycardia, and mild systolic hypertension. The lungs rapidly become overinflated, and the anteroposterior diameter of the thorax increases. If the attack is severe or prolonged, there may be a loss of adventitial breath sounds, and wheezing becomes very high pitched. Furthermore, the accessory muscles become visibly active, and a paradoxical pulse often develops. These two signs are extremely valuable in indicating the severity of the obstruction. In the presence of either, pulmonary function tends to be significantly more impaired than in their absence. It is important to note that the development of a paradoxical pulse depends on the generation of large negative intrathoracic pressures. Thus, if the patient's breathing is shallow, this sign and/or the use of accessory muscles could be absent even though obstruction is quite severe. The other signs and symptoms of asthma only imperfectly reflect the physiologic alterations that are present. Indeed, if the disappearance of subjective complaints or even of wheezing is used as the end point at which therapy for an acute attack is terminated, an enormous reservoir of residual disease will be missed.

The end of an episode is frequently marked by a cough that produces thick, stringy mucus, which often takes the form of casts of the distal airways (Curschmann's spirals) and, when examined microscopically, often shows eosinophils and Charcot-Leyden crystals. In extreme situations, wheezing may lessen markedly or even disappear, cough may become extremely ineffective, and the patient may begin a gasping type of respiratory pattern. These findings imply extensive mucus plugging and impending suffocation. Ventilatory assistance by mechanical means may be required. Atelectasis due to inspissated secretions occasionally occurs with asthmatic attacks. Spontaneous pneumothorax and/or pneumomediastinum occur but are rare.

Less typically, a patient with asthma may complain of intermittent episodes of nonproductive cough or exertional dyspnea. Unlike other individuals with asthma, when these patients are examined during symptomatic periods, they tend to have normal breath sounds but may wheeze after repeated forced exhalations and/or may show ventilatory impairments when tested in the laboratory. In the absence of both these signs, a bronchoprovocation test may be required to make the diagnosis.

DIFFERENTIAL DIAGNOSIS The differentiation of asthma from other diseases associated with dyspnea and wheezing is usually not difficult, particularly if the patient is seen during an acute episode. The physical findings and symptoms listed above and the history of periodic attacks are quite characteristic. A personal or family history of allergic diseases such as eczema, rhinitis, or urticaria is valuable contributory evidence. An extremely common feature of asthma is nocturnal awakening with dyspnea and/or wheezing. In fact, this phenomenon is so prevalent that its absence raises doubt about the diagnosis.

Upper airway obstruction by tumor or *laryngeal edema* can occa-

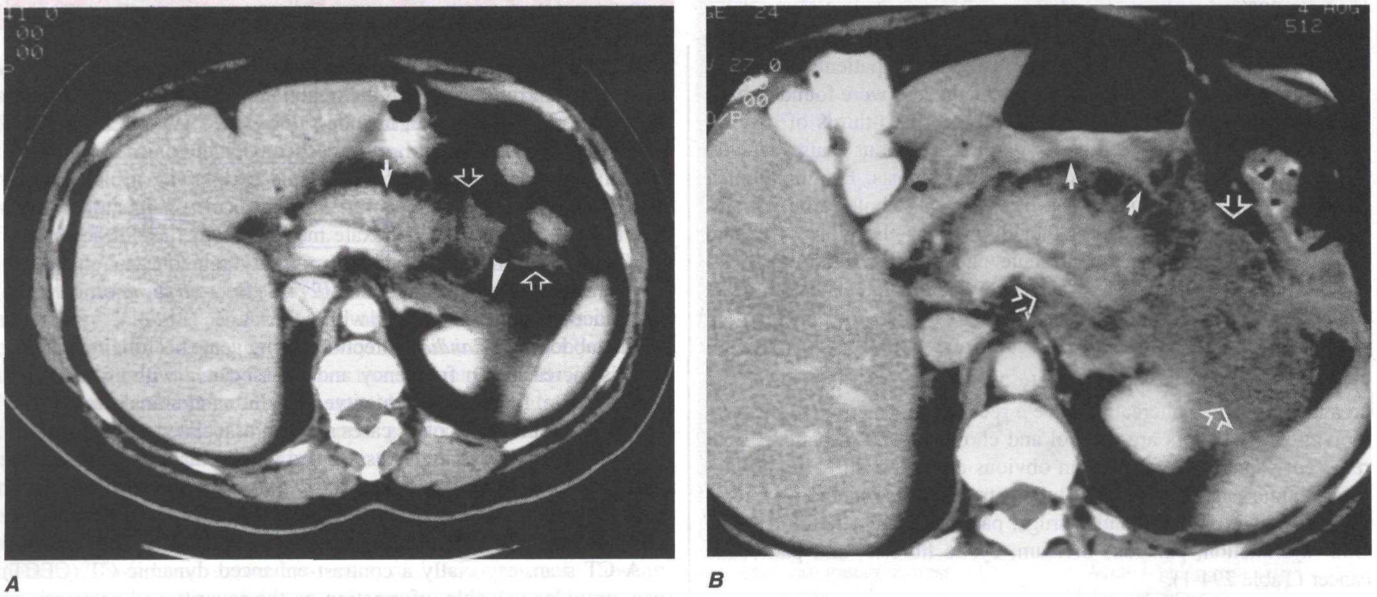

FIGURE 294-1 Acute pancreatitis: CT evolution. *A.* Contrast-enhanced CT scan of the abdomen performed on admission of a patient with clinical evidence of acute pancreatitis. Note the mildly decreased density of the body of the pancreas to the left of the midline (*arrow*). There are a few linear strands in the peripancreatic fat, suggesting inflammation (*open arrows*). A small amount of fluid is seen in the anterior pararenal space (*arrowhead*). *B.* Nine days after admission, there is a marked worsening with severe inflammation of the pancreas evidenced by anterior displacement of the posterior gastric wall (*arrows*), increased inflammation of the peripancreatic fat, and increased pancreatic effusion in the anterior perirenal space and around the splenic vein (*open arrows*). *(Courtesy of Dr. PR Ros, University of Florida College of Medicine.)*

carried out within the first 36 to 72 h of the attack. Studies indicate that only those patients with gallstone pancreatitis who are in the very severe group should be considered for urgent ERCP. Finally, the treatment for patients with hypertriglyceridemia-associated pancreatitis includes (1) weight loss to ideal weight, (2) a lipid-restricted diet, (3) exercise, (4) avoidance of alcohol and of drugs that can elevate serum triglycerides (i.e., estrogens, vitamin A, thiazides, and beta-blockers), and (5) control of diabetes.

INFECTED PANCREATIC NECROSIS, ABSCESS, AND PSEUDOCYST Infected pancreatic necrosis should be differentiated from pancreatic abscess. The former is a diffuse infection of an acutely inflamed, necrotic pancreas occurring in the first 1 to 2 weeks after the onset of pancreatitis. In contrast, a pancreatic abscess is an ill-defined, liquid collection of pus that evolves over a longer period, often 4 to 6 weeks. It tends to be less life-threatening and is associated with a lower rate of surgical mortality. Infected pancreatic necrosis should be treated by surgical debridement because the solid component of the infected pancreas is not amenable to effective radiologically guided percutaneous evacuation. Pancreatic abscess can be treated surgically or, in selected cases, by percutaneous drainage. The necrotic pancreas becomes secondarily infected in 40 to 60% of patients, most frequently with gram-negative bacteria of alimentary origin. Whether infection occurs depends on several factors, including the extent of pancreatic and peripancreatic necrosis, the degree of pancreatic ischemia and hypoperfusion, and the presence of organ or multiorgan failure.

The early diagnosis of pancreatic infection can be accomplished by CT-guided needle aspiration. In one study, 60 patients, representing 5% of all admissions for acute pancreatitis, were suspected of harboring a pancreatic infection on the basis of fever, leukocytosis, and an abnormal CT scan (pseudocyst or extrapancreatic fluid collection). Importantly, 60% of these patients had a pancreatic infection, and 55% of these infections developed in the first 2 weeks. These findings suggest that only guided aspiration can reliably distinguish sterile from infected pancreatic necrosis. The following are guidelines for patients meeting the above selection criteria: (1) Pseudocysts should be aspirated promptly, because more than half may be infected; (2) extrapancreatic fluid collections need not be aspirated promptly, because most are sterile; (3) if a necrotic pancreas is found initially to be sterile but fever and leukocytosis persist, several days of observation should be allowed to pass before reaspiration is considered, as clinical improvement frequently occurs; and (4) if fever and leukocytosis recur after an interval of well-being, reaspiration should be considered.

Severe pancreatitis with the presence of key risk factors, postoperative pancreatitis, early oral feeding, early laparotomy, and perhaps injudicious use of antibiotics predispose to the development of pancreatic abscess, which occurs in 3 to 4% of patients with acute pancreatitis. Pancreatic abscess may also develop because of a communication between a pseudocyst and the colon, inadequate surgical drainage of a pseudocyst, or needling of a pseudocyst. The characteristic signs of abscess are fever, leukocytosis, ileus, and rapid deterioration in a patient previously recovering from pancreatitis. Sometimes, however, the only manifestations are persistent fever and signs of continuing pancreatic inflammation. Drainage of pancreatic abscesses by percutaneous catheter techniques, using CT guidance, has been only moderately successful (resolution in 50 to 60% of patients). Accordingly, laparotomy with radical sump drainage and possibly resection of necrotic tissue is usually required, because the mortality rate for undrained pancreatic abscess approaches 100%. Multiple abscesses are common, and reoperation is frequently necessary.

Pseudocysts of the pancreas are collections of tissue, fluid, debris, pancreatic enzymes, and blood which develop over a period of 1 to 4 weeks after the onset of acute pancreatitis; they form in approximately 15% of patients with acute pancreatitis. In contrast to true cysts, pseudocysts do not have an epithelial lining; their walls consist of necrotic tissue, granulation tissue, and fibrous tissue. Disruption of the pancre-

TABLE 294-4 Severity Index in Acute Pancreatitis

	Points
Grade of acute pancreatitis	
Normal pancreas	0
Pancreatic enlargement alone	1
Inflammation compared with pancreas and peripancreatic fat	2
One peripancreatic fluid collection	3
Two or more fluid collections	4
Degree of pancreatic necrosis	
No necrosis	0
Necrosis of one-third of pancreas	2
Necrosis of one-half of pancreas	4
Necrosis of more than one-half of pancreas	6
CT severity index (CTSI) = CT grade + necrosis score (0–10)	

atic ductal system is common. However, the subsequent course of this disruption varies widely, ranging from spontaneous healing to continuous leakage of pancreatic juice, which results in tense ascites. Pseudocysts are preceded by pancreatitis in 90% of cases and by trauma in 10%. Approximately 85% are located in the body or tail of the pancreas and 15% in the head. Some patients have two or more pseudocysts. Abdominal pain, with or without radiation to the back, is the usual presenting complaint. A palpable, tender mass may be found in the middle or left upper abdomen. The serum amylase level is elevated in 75% of patients at some point during their illness and may fluctuate markedly.

On x-ray examination, 75% of pseudocysts can be seen to displace some portion of the gastrointestinal tract (Fig. 294-2). Sonography, however, is reliable in detecting pseudocysts. Sonography also permits differentiation between an edematous, inflamed pancreas, which can give rise to a palpable mass, and an actual pseudocyst. Furthermore, serial ultrasound studies will indicate whether a pseudocyst has resolved. CT complements ultrasonography in the diagnosis of pancreatic pseudocyst (Fig. 294-2), especially when the pseudocyst is infected.

In studies with sonography, pseudocysts were seen to resolve in 25 to 40% of patients. Pseudocysts that are >5 cm in diameter and that persist for >6 weeks should be considered for drainage. Recent natural history studies have suggested that noninterventional, expectant management is the best course in selected patients with minimal symptoms and no evidence of active alcohol use in whom the pseudocyst appears mature by radiography and does not resemble a cystic neoplasm. A significant number of these pseudocysts resolve spontaneously more than 6 weeks after their formation. Also, these studies demonstrate that large pseudocyst size is not an absolute indication for interven-

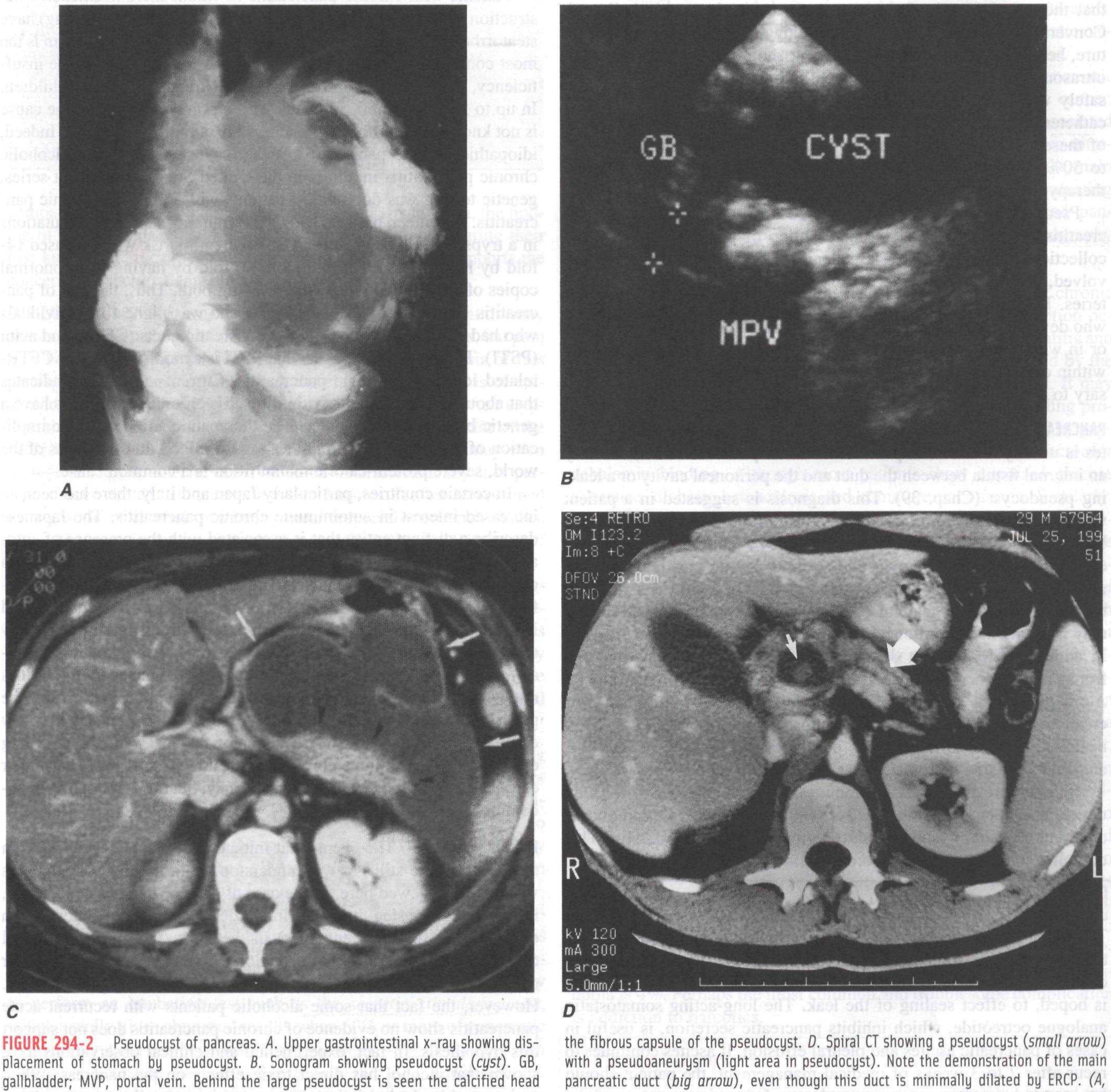

FIGURE 294-2 Pseudocyst of pancreas. *A.* Upper gastrointestinal x-ray showing displacement of stomach by pseudocyst. *B.* Sonogram showing pseudocyst (*cyst*). GB, gallbladder; MVP, portal vein. Behind the large pseudocyst is seen the calcified head of the pancreas. A dilated common bile duct (*asterisk*) is noted. *C.* CT scan showing pseudocyst. Note the large, lobulated fluid collection (*arrows*) surrounding the tail of the pancreas (*arrowheads*). Note also the dense, thin rim in the periphery representing the fibrous capsule of the pseudocyst. *D.* Spiral CT showing a pseudocyst (*small arrow*) with a pseudoaneurysm (light area in pseudocyst). Note the demonstration of the main pancreatic duct (*big arrow*), even though this duct is minimally dilated by ERCP. *(A, B courtesy of Dr. CE Forsmark, University of Florida College of Medicine; C, D courtesy of Dr. PR Ros, University of Florida College of Medicine.)*

quence of about 1000 amino acids in which glycine (Gly) appears as every third amino acid. Therefore, the sequence of each α chain can be designated as $(\text{-Gly-X-Y-})_{333}$, where X and Y represent amino acids other than glycine. To fold into a triple helix, every third amino acid in an α chain must be glycine, the smallest amino acid, since this residue must fit in a sterically restricted space where the three chains of the triple helix come together. Many of the X- and Y-position amino acids are proline and hydroxyproline, which, because of their ring structure, provide rigidity to the triple helix.

Twenty-five different collagens have been identified. Many are minor constituents that probably have highly specialized functions. The fibrillar collagens are abundant proteins that are found in tissues as long, highly ordered fibrils with a characteristic banding pattern revealed by electron microscopy. Type I collagen, the most abundant, is composed of two identical α chains called $\alpha 1(\text{I})$ and a third called $\alpha 2(\text{I})$. Type II collagen, the fibrillar collagen of cartilage, is composed of three identical α chains called $\alpha 1(\text{II})$. Type III collagen is found in small amounts in many tissues that contain type I collagen and in large amounts in large blood vessels; it is composed of three identical chains called $\alpha 1(\text{III})$. Type IV collagen in basement membranes self-assembles into a complex three-dimensional network that provides a diffusion barrier in the renal glomerulus, pulmonary alveolus, and other tissues.

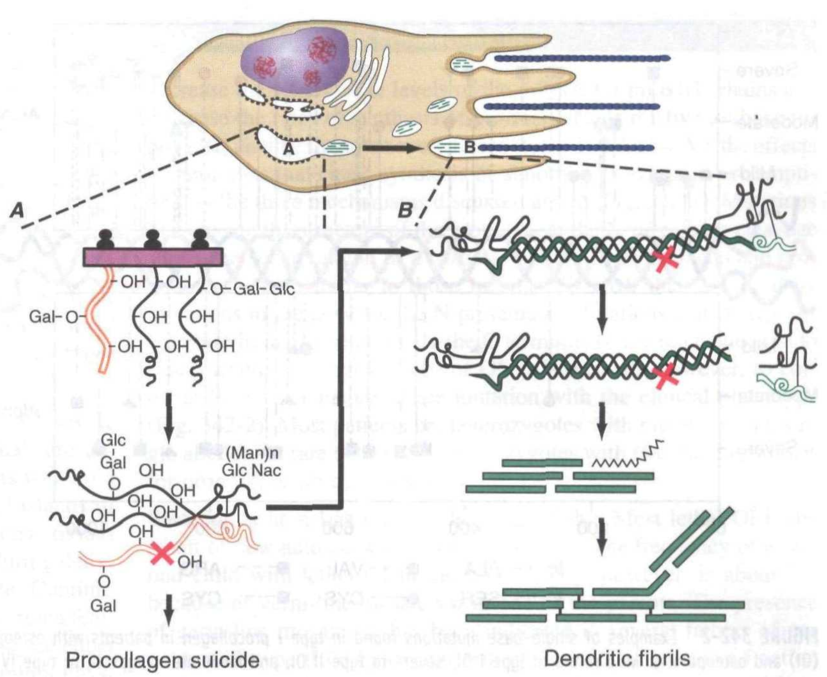

FIGURE 342-1 Schematic representation of synthesis of a type I collagen fibril by a fibroblast. *A.* Intracellular steps in the assembly of the procollagen molecule. Hydroxylations and glycosylations of the proα chains begin soon after the amino termini pass into the cisternae of the rough endoplasmic reticulum and continue after the three chains associate through their carboxy-terminal propeptides and become disulfide linked. *B.* Cleavage of procollagen to collagen, self-assembly of the collagen molecule into quarter-staggered fibrils, and cross-linking of the molecules in the fibrils. Cleavage of the propeptides may occur within crypts of the fibroblast, as shown here, or some distance from the cell. Mutations (depicted by X) cause the synthesis of structurally abnormal pro$\alpha 1(\text{I})$ or pro$\alpha 2(\text{I})$ chains of type I procollagen by interfering either with protein assembly (procollagen suicide) (*A*) or with processing to normal collagen fibrils (*B*). *(From DJ Prockop et al, Am J Med Genet 34:60, 1989, with permission.)*

Collagens are first synthesized as larger and more soluble precursors called *procollagens* that are composed of proα chains. As the proα chains of procollagen are synthesized on ribosomes, the free ends move into the cisternae of the rough endoplasmic reticulum (Fig. 342-1). Hydrophobic signal peptides at the N termini are cleaved, and additional posttranslational reactions begin. Proline residues in the Y position of the repeating -Gly-X-Y- sequences are converted to hydroxyproline by prolyl hydroxylase. The requirement for ascorbic acid as cofactor in the hydroxylation of prolyl residues explains why wounds fail to heal in scurvy (Chap. 61). If sufficient proline residues are not converted to hydroxyproline, collagen cannot fold into a triple helix that is stable at body temperature. The abnormal protein accumulates in the cisternae of the rough endoplasmic reticulum and is slowly degraded. Lysine residues in the Y position are similarly hydroxylated to hydroxylysine by lysyl hydroxylase. Many of the hydroxylysine residues are glycosylated with galactose or with galactose and glucose. A large mannose-rich oligosaccharide is assembled on the C-terminal propeptide of each chain.

After secretion, procollagen is processed to collagen by cleavage of the N-propeptides by procollagen N-proteinase and of the C-propeptides by procollagen C-proteinase. The processing converts the precursor to type I collagen and thereby decreases the solubility of the protein about 1000-fold. The entropic energy that is released drives the spontaneous self-assembly of the collagen into fibrils. Self-assembled collagen fibers have considerable tensile strength, which is increased by cross-linking reactions that form covalent bonds between α chains in one molecule and α chains in adjacent molecules. The first step in cross-linking is oxidation by lysyl oxidase of amino groups on a few lysine or hydroxylysine residues to form aldehydes that interact to form stable covalent bonds.

During growth and development, the collagen fibrils in all tissues undergo repeated synthesis, degradation, and resynthesis. The degradation of collagen fibers in tissues is initiated by specific collagenases. Collagen fibers in most tissues of normal adults undergo very little metabolic turnover. One exception to this is the collagen fibrils that are degraded and resynthesized as part of the continual remodeling of bone. Also, although the collagen in many adult tissues is metabolically stable, the rate of turnover increases under some circumstances. In starvation, a large fraction of the collagen in skin and other connective tissues is degraded, thus providing amino acids for gluconeogenesis. Large losses of collagen also occur in most connective tissues during immobilization or prolonged periods of low-gravitational stress. In rheumatoid arthritis, pannus invasion causes a rapid degradation of collagen in the articular cartilage. Glucocorticoids decrease the collagen content of most connective tissues, including bone, by decreasing the rate of collagen synthesis. Decreases in collagen weaken tissues. In many pathologic states, however, collagen is deposited in excess. With injury to tissue, inflammation is usually followed by increased deposition primarily of type I collagen fibrils in the form of fibrotic tissue and scars. The deposition of collagen fibrils during the repair process is largely irreversible and is a major feature of the pathologic changes in hepatic cirrhosis, pulmonary fibrosis, atherosclerosis, and nephrosclerosis and in the scarring of skin and ligaments after surgery or trauma.

Elastin Synthesis Elastin assembly appears to be closely related to that of collagen, since a few of the prolines in the protein are hydroxylated to hydroxyproline by prolyl hydroxylase. The elastin monomer, however, is a single polypeptide that does not fold into a defined three-dimensional structure and is not synthesized as a larger precursor molecule. Instead, it is slowly secreted from cells into extracellular compartments, where it forms amorphous deposits around previously deposited microfibrils. The elastin deposits then become covalently cross-linked through oxidation of lysine residues to aldehydes by the same lysyl oxidase that initiates the cross-linking of collagen. The microfibrils in elastin deposits are largely composed of fibrillin, a large protein that forms beadlike strands.

Proteoglycan Synthesis The synthesis of proteoglycans begins in the cisternae of the rough endoplasmic reticulum with assembly of a core protein that then undergoes sequential additions of sugars to generate large side chains of glycosaminoglycans. At least 30 proteoglycans have been identified by differences in the structures of their core proteins and their side chains. The major proteoglycan of cartilage, called

342 INHERITED DISORDERS OF CONNECTIVE TISSUE

Darwin J. Prockop, Leena Ala-Kokko

Heritable disorders that involve the major connective tissues of the body such as bone, skin, cartilage, blood vessels, and basement membranes are among the most common genetic diseases in human beings. Here we will focus primarily on those disorders that can have severe manifestations, are relatively common, and are sufficiently understood at the molecular level to provide useful paradigms: osteogenesis imperfecta (OI), the Ehlers-Danlos syndrome (EDS), chondrodysplasias (CDs), the Marfan syndrome (MFS), epidermolysis bullosa (EB), and the Alport syndrome (AS).

THE CHALLENGE OF CLASSIFYING THE DISEASES The original classification of connective tissue diseases was based on the pattern of inheritance, the cluster of signs and symptoms, the histologic changes in tissues, and limited information about the molecular defects involved. This classification included about a dozen types and subtypes for OI, about the same number for the EDS, and over 150 for the CDs. Several limitations in these original classifications are now apparent. One is that the same mutation does not always produce the same disease phenotype in terms of severity of the condition or its clinical course. Such phenotypic variation occurs in many genetic diseases, including the connective tissue disorders, in which some members of a family are severely affected, whereas others with the same mutation have a mild disorder.

Most patients with classic features of a severe connective tissue disease have a mutation in a gene, or genes, coding for a single protein. For example, the majority of patients with OI have a mutation in one of the two genes coding for type I procollagen. Similarly, most patients with MFS have mutations in a gene for fibrillin. For other disease categories, the situation is more complex. In EDS, for example, the type IV variant is usually caused by mutations in the gene for type III procollagen, the type VI variant by defects in the gene for lysyl hydroxylase, and the type VII variant by defects in a gene required for processing type I procollagen to type I collagen.

Classifications of these disorders also tend to overemphasize the etiologic differences between severe genetic diseases that are apparent in infants and the more common diseases that appear much later in life. Single-gene defects can cause subsets of late-onset diseases such as osteoporosis, aneurysms, and osteoarthritis. For example, a small subset of patients with postmenopausal osteoporosis have mutations in the genes for procollagen I similar to the mutations in the same genes that produce lethal variants of OI. Likewise, a subset of patients with familial aortic aneurysms have mutations in the gene for procollagen III similar to the mutations in the same gene that cause lethal variants of type IV EDS, and occasional patients with osteoarthritis have mutations in the gene for procollagen II similar to the mutations in the same gene that cause lethal CDs.

DEFINITION AND COMPOSITION OF CONNECTIVE TISSUES The distinguishing feature of connective tissues is that it consists of complex macromolecules that are assembled into an insoluble extracellular matrix (Table 342-1). The macromolecules include at least 25 different types of collagens, the related fibrous proteins known as *elastin* and *fibrillin*, a series of proteoglycans, and other components whose structure and function are only partially defined. Differences in the connective tissues of bone, skin, and cartilage are partially explained by differences in the content of specific components (Table 342-1). For example, tendons and ligaments consist primarily of type I collagen fibrils and small amounts of other components that help organize the type I fibrils into thick fibers and fiber bundles. Cartilage consists primarily of fibrils of type II collagen in the form of arcades that are distended by highly charged proteoglycans. The extracellular matrix of the aorta contains collagens that provide tensile strength and elastin that provides elasticity. Differences among the connective tissues also depend on the three-dimensional organization of the molecular components. The type I collagen fibrils in tendon are packed into thick, parallel bundles of fibers, whereas type I collagen fibrils in skin are randomly oriented. In cortical bone, type I collagen fibrils form helical arrays around haversian canals.

BIOSYNTHESIS OF CONNECTIVE TISSUE Connective tissues form primarily by a process of self-assembly, in which a molecule of the correct size, shape, and surface property binds to other molecules with the same or similar structure in a spontaneous and precisely ordered manner. The molecular mechanisms and driving forces are similar to those involved in crystal formation.

Collagen Synthesis Collagens have a triple-helical conformation, because each of the three α chains has a simple, repetitive amino acid se-

TABLE 342-1 *Constituents of Connective Tissues in Various Tissues*

Connective Tissue	*Major Constituents*	*Approximate Amounts, % dry wt*	*Characteristics or Functions*
Dermis, ligaments, tendons	Type I collagen	80	Bundles of fibrils
	Type III collagen	5–15	Thin fibrils
	Type IV collagen, laminin, nidogen	<5	In basal laminae under epithelium and endothelium
	Types V, VI, and VII collagens	<5	VII forms anchoring fibrils; others unknown
	Elastin, fibrillin	<5	Provides elasticity
	Fibronectin	<5	Associated with collagen fibers and cell surfaces
	Proteoglycans,[a] hyaluronate	0.5	Provide resiliency
Bone (demineralized)	Type I collagen	90	Complex fibril network
	Type VI collagen	1–2	Function unclear
	Proteoglycans[a]	1	Function unclear
	Osteonectin, osteopontin, osteocalcin, α2-glycoprotein, sialoproteins	1–5	May regulate mineralization
Aorta	Type I collagen	20–40	Fibril network
	Type III collagen	20–40	Thin fibrils
	Elastin, fibrillin	20–40	Provide elasticity
	Type IV collagen, laminin, nidogen	<5	Form basal lamina
	Types V and VI collagens	<2	Functions unclear
	Proteoglycans[a]	<3	Provide resiliency
Cartilage	Type II collagen	40–50	Arcades of thin fibrils
	Type IX collagen	5–10	Links type II fibrils
	Type X collagen	5–10	Surrounds hypertrophic cells
	Type XI collagen	<10	Function unclear
	Proteoglycans,[a] hyaluronate	15–50	Provides resiliency

[a] As discussed in text, >30 proteoglycans have now been identified. They differ in the structures of their core proteins and their contents of glycosaminoglycan side chains of chondroitin-4-sulfate, chondroitin-6-sulfate, dermatan sulfate, and keratin sulfate. Basal lamina contain a proteoglycan with a side chain of heparan sulfate that resembles heparin.

TABLE A-2 *Immunology—(Continued)*

Analyte	Specimen	SI Units	Conventional Units
C-reactive protein	S		
Routine		0.08–3.1 mg/L	0.08–3.1 mg/L
High sensitivity		0.02–8.0 mg/L	0.02–8.0 mg/L
C1-esterase-inhibitor protein	S		
Antigenic		0.12–0.25 g/L	12.4–24.5 mg/dL
Functional		Present	Present
Complement			
C3 (adults)	S	0.86–1.84 g/L	86–184 mg/dL
C4 (adults)	S	0.20–0.58 g/L	20–58 mg/dL
Total complement, EIA (adult)	S	63–145 kU/L	63–145 U/mL
Factor B	S	0.17–0.42 g/L	17–42 mg/dL
Cryoproteins	S	Not applicable	None detected
Immunofixation	S	Not applicable	None detected
Immunoglobulin, quantitation (adult)			
IgA	S	0.60–3.09 g/L	60–309 mg/dL
IgD	S	0–140 mg/L	0–14 mg/dL
IgE	S	24–430 μg/L	10–179 IU/mL
IgG	S	6.14–12.95 g/L	614–1295 mg/dL
IgG_1	S	2.7–17.4 g/L	270–1740 mg/dL
IgG_2	S	0.3–6.3 g/L	30–630 mg/dL
IgG_3	S	0.13–3.2 g/L	13–320 mg/dL
IgG_4	S	0.11–6.2 g/L	11–620 mg/dL
IgM	S	0.53–3.34 g/L	53–334 mg/dL
Joint fluid crystal	JF	Not applicable	No crystals seen
Joint fluid mucin	JF	Not applicable	Only type I mucin present
LE cell test	WB	Negative	Negative
Rheumatoid factor	S, JF	<30 kIU/L	<30.0 IU/mL
Serum protein electrophoresis	S	Not applicable	Normal pattern

Note: JF, joint fluid; P, plasma; S, serum; U, urine; WB, whole blood

TABLE A-3 *Clinical Chemistry*

Constituent	Specimen	SI Units	Conventional Units
Acetoacetate	P	<100 μmol/L	<1 mg/dL
Albumin	S	35–55 g/L	3.5–5.5 g/dL
Aldolase	S	0–100 nkat/L	0–6 U/L
α_1 antitrypsin	S	0.8–2.1 g/L	85–213 mg/dL
Alpha fetoprotein (adult)	S	<15 μg/L	<15 ng/mL
Aminotransferases	S		
Aspartate (AST, SGOT)		0–0.58 μkat/L	0–35 U/L
Alanine (ALT, SGPT)		0–0.58 μkat/L	0–35 U/L
Ammonia, as NH_3	P	6–47 μmol/L	10–80 μg/dL
Amylase	S	0.8–3.2 μkat/L	60–180 U/L
Angiotensin-converting enzyme (ACE)	S	<670 nkat/L	<40 U/L
Anion gap	S	7–16 mmol/L	7–16 mmol/L
Apolipoprotein A-1	S	1.2–2.4 g/L	119–240 mg/dL
Apolipoprotein B	S	0.52–1.63 g/L	52–163 mg/dL
Apo B/Apo A-1 ratio		0.35–0.98	0.35–0.98
Arterial blood gases			
$[HCO_3^-]$		21–28 mmol/L	21–30 meq/L
P_{CO_2}		4.7–5.9 kPa	35–45 mmHg
pH		7.38–7.44	
P_{O_2}		11–13 kPa	80–100 mmHg
β-Hydroxybutyrate	P	<300 μmol/L	<3 mg/dL
β-2-microglobulin	S	1.2–2.8 mg/L	1.2–2.8 mg/L
	U	≤200 μg/L	≤200 μg/L
Bilirubin	S		
Total		5.1–17 μmol/L	0.3–1.0 mg/dL
Direct		1.7–5.1 μmol/L	0.1–0.3 mg/dL
Indirect		3.4–12 μmol/L	0.2–0.7 mg/dL
Brain type natriuetic peptide (BNP)	P	Age and gender specific: <167 ng/L	Age and gender specific: <167 pg/mL
Calcium, ionized	WB	1.1–1.4 mmol/L	4.5–5.6 mg/dL
Calcium	S	2.2–2.6 mmol/L	9–10.5 mg/dL
CA-15-3	S	0–30 kU/L	0–30 U/mL
CA 19-9	S	0–37 kU/L	0–37 U/mL
CA 27-29	S	0–32 kU/L	0–32 U/mL
CA 125	S	0–35 kU/L	0–35 U/mL
Calcitonin	S		
Male		3–26 ng/L	3–26 pg/mL
Female		2–17 ng/L	2–17 pg/mL

(continued)

TABLE A-3—(Continued)

Constituent	Specimen	SI Units	Conventional Units
Carbon dioxide content (TCO_2)	P (sea level)	21–30 mmol/L	21–30 meq/L
Carbon dioxide tension (P_{CO_2})	Arterial blood (sea level)	4.7–5.9 kPa	35–45 mmHg
Carbon monoxide content	WB	Symptoms with 20% saturation of hemoglobin	
Carcinoembryonic antigen (CEA)	S	0.0–3.4 ug/L	0.0–3.4 ng/mL
Ceruloplasmin	S	270–37 mg/L	27–37 ng/dL
Cholinesterase	S	5–12 kU/L	5–12 U/mL
Chloride	S	98–106 mmol/L	98–106 meq/L
Cholesterol: see Table A-7			
Coproporphyrins (types I and III)	U	150–460 μmol/d	100–300 μg/d
C-peptide	S	0.17–0.66 nmol/L	0.5–2.0 ng/mL
Creatine kinase (CK) (total)	S		
Females		0.67–2.50 μkat/L	40–150 U/L
Males		1.00–6.67 μkat/L	60–400 U/L
Creatine kinase-MB	S	0–7 μg/L	0–7 ng/mL
Creatine kinase relative index (ng/mL per total CK U/L) × 100	S	Method dependent	Method dependent
Creatinine	S	<133 μmol/L	<1.5 mg/dL
Erythropoietin	S	5–36 U/L	
Fatty acids, free (nonesterified)	P	0.28–0.89 mmol/L	<8–25 mg/dL
Ferritin	S		
Female		10–200 μg/L	10–200 ng/mL
Male		15–400 μg/L	15–400 ng/mL
Fibrinogen and fibrinogen split products: see Hematology and Coagulation			
Gamma glutamyltransferase	S	1–94 U/L	1–94 U/L
Glucose (fasting)	P		
Normal		4.2–6.4 mmol/L	75–115 mg/dL
Diabetes mellitus		>7.0 mmol/L	>125 mg/dL
Glucose, 2 h postprandial	P	<6.7 mmol/L	<120 mg/dL
Hemoglobin A_{1c}	WB	0.038–0.064 Hb fraction	3.8–6.4%
Homocysteine	P	4–12 μmol/L	4–12 μmol/L
Hydroxyproline	U, 24 hour	0–10 μmol/L	0–1.3 mg/d
Iron	S	9–27 μmol/L	50–150 μg/dL
Iron-binding capacity	S	45–66 μmol/L	250–370 μg/dL
Iron-binding capacity saturation	S	0.2–0.45	20–45%
Ketone (acetone)	S, U	Negative	Negative
Lactate dehydrogenase	S	1.7–3.2 μkat/L	100–190 U/L
Lactate	P, venous	0.6–1.7 mmol/L	5–15 mg/dL
Lactate dehydrogenase isoenzymes	S		
Fraction 1 (of total)		0.14–0.25	14–26%
Fraction 2		0.29–0.39	29–39%
Fraction 3		0.20–0.25	20–26%
Fraction 4		0.08–0.16	8–16%
Fraction 5		0.06–0.16	6–16%
Lipase	S	0–2.66 μkat/L	0–160 U/L
Lipids: see Table A-7			
Lipids, triglyceride: see Triglycerides			
Lipoprotein: see Table A-7			
Lipoprotein (a)	S	0–300 mg/L	0–30 mg/dL
Magnesium	S	0.8–1.2 mmol/L	1.8–3 mg/dL
Microalbumin urine			
24-h urine	U	<0.2 g/L or <0.031 g/24 h	<20 mg/L or <31 mg/24 h
Spot AM urine		<0.03 g albumin/g creatinine	<0.03 mg albumin/mg creatinine
Myoglobin	S		
Male		19–92 μg/L	
Female		12–76 μg/L	
5 Nucleotidase	S	0.02–0.18 ukat/L	0–11 U/L
N-telopeptide (cross linked), NTx	U	3–65 nmol/mmol creatinine	3–65 nmol/mmol creatinine
Osmolality			
	P	285–295 mmol/kg serum water	285–295 mosmol/kg serum water
	U	300–900 mmol/kg	300–900 mosmol/kg
Osteocalcin	S	3.1–14 ug/mL	3.1–14 ng/mL
Oxygen content	WB, arterial (sea level)		17–21 vol%
	WB, venous arm (sea level)		10 to 16 vol%
Oxygen percent saturation (sea level)			
	WB, arterial	0.97 mol/mol	97%
	WB, venous, arm	0.60–0.85 mol/mol	60–85%
Oxygen tension (P_{O_2})	WB	11–13 kPa	80–100 mmHg
pH	WB	7.38–7.44	
Parathyroid hormone–related peptide	S	<1.3 pmol/L	<1.3 pmol/L
Phosphatase, acid	S	0.90 nkat/L	0–5.5 U/L
Phosphatase, alkaline	S	0.5–2.0 nkat/L	30–120 U/L

(continued)

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